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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,983	10/31/2001	Hans Josef Stauss	ICI 103	6029

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/003,983	STAUSS ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-6 and 8-42* is/are pending in the application.

4a) Of the above claim(s) *5, 8-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 3/21/07 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (claims 2-4, 6 and 42), and species of SEQ ID NO: 1 containing peptide bonds in Applicant's response filed 2/2/05.

Claims 2-4, 6 and 42 read on the elected species, SEQ ID NO: 1, and are presently being examined.

The following grounds of rejection remain.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 2-4, 6 and 42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/26328 A1 (IDS reference) in view of The Leukocyte Antigen Fact Book (2nd edition, pages 244-247, 1997, IDS reference), Rammensee *et al* (MHC Ligands and Peptide Motifs, LANDES Bioscience, Springer, NY, 1997, pages 217-227 and 236-281, of record), WO 99/45954 A1, US 7,063,854 B1 and Sievers (Curr. Opin. Immunol. 12: 30-35,1/00).

WO 97/26328 A1 teaches a method of treating a disease, including leukemia, comprising administering allo-restricted allogeneic CTL specific for peptides from self proteins, for example from WT1, that are expressed in tumors and in a limited number of normal cells, tissue-specific differentiation antigens, and in the case of leukemia CTL with specificity for leukemias can be generated against peptides that are expressed in leukemic cells but not in cells outside the hematopoietic lineage and then used for adoptive immunotherapy of leukemia patients where they will eliminate leukemic cells and possibly some normal bone marrow derived cells. WO 97/26328 A1 teaches that possible loss of normal bone marrow cells is not expected to cause any problems because these patients are frequently treated with bone marrow transplantation from healthy donors (see entire article, especially page 19 at lines 21-30 and continuing onto page 20 at lines 1-5 and page 23 at lines 11-19). WO 97/26328 A1 further teaches that known CTL epitope peptides or newly identified peptides may be used, in the latter instance, the peptides that bind to a particular HLA class I molecule may be identified and may represent better targets for adoptive immunotherapy since they are likely to be subdominant peptides that are less likely to be immunoselected by the patient's CTL responses. WO 97/26328 A1 teaches methods for generating said CTL, and that the

stimulator cell has a type of HLA class I molecule that is not present on the healthy individual's cells, and further teaches testing of binding to HLA class I molecules and for generating and stimulating CTL. WO 97/26328 A1 teaches that HLA-A0201 is particularly preferred allele that is present on the stimulator cells at a high frequency in the human population (page 27 at lines 19-30 and page 28 at line 1).

WO 97/26328 A1 does not teach the CD45 peptides recited in the instant claims 2-4, 6 and 42 that consist of or comprise SEQ ID NO: 1.

The Leukocyte Antigen Fact Book teaches that CD45 protein(s) are found on all cells of hematopoietic origin, except erythrocytes, and further teaches the amino acid sequence of the human CD45 protein and that it is 1281 amino acid residues in length.

Rammensee *et al* teach anchor residue motifs for peptides that bind to individual class I MHC molecules (HLA in humans) including HLA-A*0201, and that most peptides that bind class I molecules are between 8 and 11 amino acid residues in length consonant with the length of peptide required to span the class I MHC binding groove. Rammensee *et al* teach methods of predicting MHC class I peptide epitopes using motifs to identify subsequences possessing the motif in proteins of interest. Rammensee *et al* further teach that their own motif patterns to calculate the probabilities of peptides from a given protein to be presented by MHC class I, and assign numerical values to coefficients corresponding to each position in the peptide, such as for example, for anchor residues "10" for frequently occurring residues, "8" for amino acid residues present in a significant portion of the ligands and "6" for the rarely occurring amino acid residues, and for auxiliary anchor residues "6" for frequently occurring residues, and "4" for less frequent residues, for preferred residues coefficients of "1"-"4", and negative values for unfavorable residues. Rammensee *et al* teach that the motif for peptides that bind to HLA-A*0201 is L or M at position 2 of the peptide and V or L at the carboxy-terminal position of the peptide, but that other endogenous peptides as well as CTL epitope peptides that bind to HLA-A*0201 may have I, T, M or A at position 2 as well, and A, I, T, S or C at the carboxy-terminus. Rammensee *et al* teach that most peptides that bind to HLA-A*0201 are 9 to 10 amino acid residues in length (pages 221-227 and 236-281).

WO 99/45954 A1 teaches methods for selecting immunogenic peptides capable of specifically binding HLA molecules and inducing T cell activation (abstract). WO 99/45954 A1 teaches identifying peptides from target proteins that are capable of binding to an HLA molecule by using the binding motif for a particular class I HLA molecule to search for peptides having the motif. WO 99/45954 A1 teaches testing the peptides for binding to said HLA molecule and teaches methods for said testing. WO 99/45954 A1 further teaches assaying the binding peptides for their ability to induce specific CTL responses *in vitro*, and methods for said assaying, and testing the CTL for their ability to lyse target cells. WO 99/45954 A1 teaches that HLA-A2.1 (*i.e.*, HLA-

A*0201) is expressed at high frequency in Caucasoid and Asian populations (pages 7-8, page 10 at lines 13-32, page 11, page 12 at lines 1-12).

US 7,063,854 B1 discloses immunogenic compositions comprising MHC class I binding peptides from WT1 tumor antigen protein that stimulate CTL, and that may further comprise MHC class II binding peptides that stimulate Th (*i.e.,* Th provide help for antibody production and for CTLp). US 7,063,854 B1 discloses that the pharmaceutical compositions may comprise WT1 peptides that can elicit both CD4+ and CD8+ (*i.e.,* Th and CTL) responses. US 7,063,854 B1 further discloses that a CD45 peptide antigen is capable of stimulating T cells, as well as disclosing prediction of HLA-A*0201 binding peptides that are potentially capable of binding and eliciting CTL and prediction of T cell epitope peptides that potentially function as Th epitopes. US 7,063,854 B1 discloses peptides that tested positive for binding to HLA-A*0201 and were capable of eliciting a CTL response (especially abstract, column 28 at lines 53-64, column 29, column 30 at Table III, column 61, claims, column 18 at lines 27-67, column 19, column 20 at lines 1-61, column 29 at lines 1-16).

Sievers teaches that CD45 is a target antigen for the majority of leukemia cells as well as for normal stem cells, and an antibody specific for CD45 is useful in combination with conventional preparative regimens for patients receiving marrow transplantation for acute leukemia, as well as for targeting radiation *in vivo* (especially abstract, last paragraph of article, page 33 at column 2 and page 34 through the first full paragraph at column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of epitope prediction taught by Rammensee *et al* and WO 99/45954 A1 using the peptide binding motif of a frequently expressed HLA molecule such as HLA-A*0201, and including using the predictive algorithms taught by Rammensee *et al* to scan the human CD45 protein sequence taught by The Leukocyte Antigen Fact Book and by Sievers for subsequences that would potentially bind to HLA-A0201 and function to stimulate CTL as taught by Rammensee *et al* and by WO 97/26328 A1, in effect to generate peptides of 9 amino acid residues in length that would be predicted to bind to HLA-A*0201 from the sequence of human CD45 protein, said peptides having the motif anchor residues at positions 2 and 9 or 10, and to have produced the peptides recited in the instant claims comprising or consisting of SEQ ID NO: 1 which is a subsequences of human CD45 that has the anchor residues taught by Rammensee *et al*, and to have tested synthetic peptide versions of them as per the teaching of WO 99/45954 A1 for binding to HLA-A*0201 and for their ability to stimulate CTL, and as per the teaching of WO 97/26328 A1 for identifying peptides that bind to a particular HLA class I molecule from differentiation antigens such as WT-1 expressed in leukemic cells or from proteins expressed in leukemic cells but not in cells outside the hematopoietic lineage.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the said peptides and tested them for potential use in the method taught by WO 97/26328 A1 for generating allo-restricted CTL for use in adoptive immunotherapy of leukemia patients.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to generate peptides as per the teaching of Rammensee *et al* and WO 99/45954 A1 using the human CD45 protein sequence taught by The Leukocyte Antigen Fact Book that are candidate peptides for binding HLA-A*0201 and for stimulating CTL as taught by WO 99/45954 A1 for potential use in the method taught by WO 97/26328 A1 of identifying peptides that can bind to alleles present in high frequency in the population such as HLA-A0201 for generation of allo-restricted CTL that are useful in treating leukemia patients. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 97/26328 A1 teaches that allo-restricted CTL that are specific for peptides that are expressed on leukemic cells but not in cells outside the hematopoietic lineage are useful to treat patients with leukemia and that such a use is not expected to cause any problems due to possible loss of normal bone marrow cells because these patients are frequently treated with bone marrow transplantation from healthy donors and further teaches using WT1 peptides, The Leukocyte Antigen Fact Book teaches that the human CD45 protein is found on all cells of hematopoietic origin, Sievers teaches that CD45 is a target antigen for the majority of leukemia cells as well as for normal stem cells and the usefulness of targeting CD45 to treat leukemia, and US 7,063,854 B1 discloses that CD45 peptide is capable of eliciting a CTL response and pharmaceutical compositions comprising peptides from another leukemia antigen WT1 that bind to class I or class II MHC to treat leukemia.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in Applicant's said amendment filed 3/21/07 on pages 8-24 under the section entitled "Rejection Under 35 U.S.C. 103."

It is the Examiner's position that the references are being argued separately. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It is the Examiner's further position that WO 97/26328 A1 does not teach away from using membrane bound cytokine receptors such as CD45 just because it teaches other proteins that are intracellular DNA binding proteins, and Sievers teaches that CD45 is a target antigen for the majority of leukemia cells. It is the Examiner's position that motivation for combining the prior art elements may be found in the teaching of Sievers who teaches that CD45 is a target antigen for the majority of leukemia cells, the

disclosure of '854 that a CD45 peptide can stimulate T cells, and in the disclosure of WO 97/26328 A1 that teaches adoptively transferring CTL with specificity for leukemias, said CTL generated against peptides that are expressed in leukemic cells but not in cells outside the hematopoietic lineage (as is CD45) and further teaches identifying new peptides that bind to a particular HLA class I molecule. '510 and '854 disclose that it is routine in the art to predict HLA-A2 binding peptides, test them for binding to HLA-A2 and for their ability to stimulate CTL.

It is the Examiner's position that Rammensee *et al* do not teach away from a position 9 anchor residue that is "T" because Rammensee *et al* teach that the motif for peptides that bind to HLA-A*0201 is L or M at position 2 of the peptide and V or L at the carboxy-terminal position of the peptide, but that other endogenous peptides as well as CTL epitope peptides that bind to HLA-A*0201 may have I, T, M or A at position 2 as well, and A, I, T, S or C at the carboxy-terminus, for example, MLDLQPETT that has a position 9 "T" anchor amino acid residue. In addition, Rammensee *et al* teach that in addition to the "L" anchor residue at position 2 (*i.e.,* P2) as a preferred anchor amino acid residue, other preferred residues include P1 "F", P3 "Y", P4 "D", P5 "V", P6 "I", P7 "A" and P8 "S", all of which are present in Applicant's claimed peptide "FLYDVIAST." In addition, Rammensee *et al* recognize that not all immunogenic peptides follow the motif and teach a predictive building up method that takes into consideration residues at all positions of the peptide sequence. It is the Examiner's position that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed peptide because the claimed peptide is a subsequence of CD45 that has a preferred P2 anchor residue as well as preferred residues at other non primary anchor positions in the peptide.

In addition, Applicant made an admission in Applicant's amendment and response filed 7/11/06, that the principles disclosed in Rammensee *et al* are provided on the internet at syfpeithi.dc/Scripts/MHCServer.dll/EpitopePrediction.htm. Applicant argued that Applicant inserted the sequence for human CD45 into the program and searched for peptides of 10 residues in length that bind HLA-A*0201 and generated hundreds of peptides (previously filed with amendment and response filed 11/21/05). The Examiner inserted the sequence for human CD45 into said program and searched for peptides of 9 amino acid residues in length, as is the claimed peptide, and the said claimed peptide FLYDVIAST had the sixth highest score over hundreds of peptides generated. Applicant argues in the instant amendment filed 3/21/07 that the Examiner appears to be arguing that one of ordinary skill in the art would have synthesized peptides corresponding to all of the predicted sequences and tested each of them for ability to bind to HLA-A*0201 and for their ability to generate CTLs. Applicant further argues that this is not the case because of the high level and cost of the work involved, and that the identification of FLYDVIAST by the inventors was a two year research project at the approximate cost of $275,000. Applicant argues that for one of ordinary skill in the art to have synthesized each of the many peptides predicted by one of the methods of epitope prediction and assessed each one for their ability to bind HLA-A2 and stimulate

CTL would have been prohibitively expensive and require undue experimentation. In response, it is the Examiner's position that "Time and difficulty of experiments are not determinative if they are merely routine." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404, and the secondary references US 7,063,854 B1 and Rammensee *et al* establish that such prediction and testing were routine in the art at the time the invention was made. In addition, In *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), cert. Denied, 490 U.S. 1046 (1989), the court reversed the findings of the district court for lack of clear and convincing proof that undue experimentation was needed. The question of time and expense of studies, approximately $50,000 and 6-12 months standing alone, failed to show undue experimentation. As enunciated above, predictive methods, including those taught by Rammensee *et al*, establish that the claimed peptide has one favorable anchor amino acid residue as well as favorable residues at other positions in the peptide, and the SYPETHEI program upon which the Rammensee *et al* algorithm is based, as admitted by Applicant, demonstrates that the claimed peptide is among the highest ranking peptides predicted.

It is the Examiner's position that WO 99/45954 A1 is being argued separately by Applicant. Although WO 99/45954 A1 teaches a motif for peptides that bind HLA-A2.1, Rammensee *et al* also teach a motif for peptides that bind HLA-A2.1 and that some HLA-A2.1 binding peptides have "T" at their carboxy-terminus. In addition, with regard to Applicant's argument that WO 99/45954 A1 teaches that the only conservative substitution involving "T" is "S", and consequently replacing the C-terminal amino acid residue V, I, L, A or M with T would be a non-conservative change that is expected to lead to a substantial change in function, *e.g.*, affinity for MHC, it is the Examiner's position that Rammensee *et al* teach that the entire sequence of the peptide contributes to peptide binding and affinity, and that some HLA-A2.1 binding peptides have "T" at the carboxy-terminus. In addition, WO 99/45954 A1 teaches that L, I, V, A and T can be anchor residues at position 2, and in common, L, I, V and A can be anchor residues at the carboxy-terminal position. The claimed peptide is not produced by substitution of T for V, I, L, A or M in a peptide, but rather by selecting a peptide subsequence of human CD45 that has T at the carboxy-terminus.

It is the Examiner's position that Sievers teaches that CD45 is a target antigen on leukemia cells, and '854 teaches a CD45 peptide that can generate a Th response presumably to provide T cell help for antibody production as well as for CTLp to CTL stimulation and '854 further teaches peptides from another leukemia cell target antigen that are Th or CTL epitopes.

With regard to Applicant's arguments to the variants of SEQ ID NO: 1, said variants are non-elected species and have not been examined.

5. Claims 2-4, 6 and 42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/26328 A1 (IDS reference) in view of The Leukocyte Antigen Fact Book (2nd edition, pages 244-247, 1997, IDS reference), LANDES Bioscience, Springer, NY, 1997, pages 217-227 and 236-281, of record), U.S. Patent No. 6,602,510 B1 (of record), U.S. Patent No. 7,063,854 B1 and Sievers (Curr. Opin. Immunol. 12: 30-35, 1/00).

WO 97/26328 A1 teaches a method of treating a disease, including leukemia, comprising administering allo-restricted allogeneic CTL specific for peptides from self proteins, for example WT1, that are expressed in tumors and in a limited number of normal cells, tissue-specific differentiation antigens, and in the case of leukemia, CTL with specificity for leukemias can be generated against peptides that are expressed in leukemic cells but not in cells outside the hematopoietic lineage and then used for adoptive immunotherapy of leukemia patients where they will eliminate leukemic cells and possibly some normal bone marrow derived cells. WO 97/26328 A1 teaches that possible loss of normal bone marrow cells is not expected to cause any problems because these patients are frequently treated with bone marrow transplantation from healthy donors (see entire article, especially page 19 at lines 21-30 and continuing onto page 20 at lines 1-5 and page 23 at lines 11-19). WO 97/26328 A1 further teaches that known CTL epitope peptides or newly identified peptides may be used, in the latter instance, the peptides that bind to a particular HLA class I molecule may be identified and may represent better targets for adoptive immunotherapy since they are likely to be subdominant peptides that are less likely to be immunoselected by the patient's CTL responses. WO 97/26328 A1 teaches methods for generating said CTL, and that the stimulator cell has a type of HLA class I molecule that is not present on the healthy individual's cells, and further teaches testing of binding to HLA class I molecules and for generating and stimulating CTL. WO 97/26328 A1 teaches that HLA-A0201 is particularly preferred allele that is present on the stimulator cells at a high frequency in the human population (page 27 at lines 19-30 and page 28 at line 1).

WO 97/26328 A1 does not teach the CD45 peptides recited in the instant claims 2-4, 6 and 42.

The Leukocyte Antigen Fact Book teaches that CD45 protein(s) are found on all cells of hematopoietic origin, except erythrocytes, and further teaches the amino acid sequence of the human CD45 protein and that it is 1281 amino acid residues in length.

U.S. Patent No. 6,602,510 B1 discloses that peptides that bind to HLA class I molecules are about 8 to about 13 amino acid residues in length and possess amino acid residues at certain positions in the peptide sequence that are required for allele-specific binding. U.S. Patent No. 6,602,510 B1 discloses that a supertype motif is a peptide binding specificity shared by HLA molecules encoded by two or more HLA alleles, and that vaccines which bind to HLA supertypes such as A2, A3 and B7 will afford broad, non-ethnically biased population coverage. U.S. Patent No. 6,602,510 B1 discloses that the

HLA-A2 supermotif is L, I, V, M, A, T or Q at position 2 of the peptide, and I, V, M, A, T or L at the carboxy-terminus of the peptide. U.S. Patent No. 6,602,510 B1 discloses that 9-mer subsequences of tumor-associated antigenic proteins were scanned to identify potential HLA-A2 supertype allele binding peptides, *i.e.,* that would bind to HLA-A0201 as well as other alleles in the supertype and synthesis and testing for binding and CTL stimulating activity, as well as a correlation of affinity with immunogenicity (especially detailed description of the invention, column 18 at lines 34, column 2 at lines 58-column 3 at lines 1-3, column 13 at lines 11-15, Table 2 and 2A, Table 4).

US 7,063,854 B1 discloses immunogenic compositions comprising MHC class I binding peptides from WT1 tumor antigen protein that stimulate CTL, and that may further comprise MHC class II binding peptides that stimulate Th (*i.e.,* Th provide help for antibody production and for CTLp). US 7,063,854 B1 discloses that the pharmaceutical compositions may comprise WT1 peptides that can elicit both CD4+ and CD8+ (*i.e.,* Th and CTL) responses. US 7,063,854 B1 further discloses that a CD45 peptide antigen is capable of stimulating T cells, as well as disclosing prediction using a predictive algorithm of HLA-A*0201 binding peptides that are potentially capable of binding and eliciting CTL and prediction of T cell epitope peptides that potentially function as Th epitopes. US 7,063,854 B1 discloses peptides that tested positive for binding to HLA-A*0201 and were capable of eliciting a CTL response (especially abstract, column 28 at lines 39-64, column 29, column 30 at Table III, column 61, claims, column 18 at lines 27-67, column 19, column 20 at lines 1-61).

Sievers teaches that CD45 is a target antigen for the majority of leukemia cells as well as for normal stem cells, and an antibody specific for CD45 is useful in combination with conventional preparative regimens for patients receiving marrow transplantation for acute leukemia, as well as for targeting radiation *in vivo* (especially abstract, last paragraph of article, page 33 at column 2 and page 34 through the first full paragraph at column 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of epitope prediction disclosed by U.S. Patent No. 6,602,510 B1 and US 7,063,854 B1 for peptides that bind to a frequently expressed HLA molecule such as HLA-A*0201 to scan the sequence of the human CD45 leukemia tumor/differentiation antigen taught by Sievers to be a target for treatment of leukemia having the sequence taught by The Leukocyte Antigen Fact Book, in a manner similar to that disclosed by US 7,063,854 B1 for the WT1 leukemia antigen to identify subsequences that would potentially bind to HLA-A*0201 and function to stimulate CTL as disclosed by U.S. Patent No. 6,602,510 B1 and as taught by WO 97/26328 A1, in effect to generate peptides of 9 or 10 amino acid residues in length that would be predicted to bind to HLA-A*0201 from the sequence of human CD45 protein, said peptides having the motif anchor residues at positions 2 and 9 or 10, and to have produced the peptides recited in the instant claims comprising or consisting

of SEQ ID NO: 1 which is a subsequences of human CD45 that has the anchor residues disclosed by U.S. Patent No. 6,602,510 B1.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have identified peptides of appropriate length and motif potentially capable of binding to an HLA-A*0201 class I MHC molecule as per the disclosure of U.S. Patent No. 6,602,510 B1 from the CD45 human protein taught by Siever with the protein sequence taught by The Leukocyte Antigen Fact Book and to have tested synthetic peptide versions of them as per the teaching of WO 97/26328 A1 and as per the disclosure of U.S. Patent No. 6,602,510 B1 and US 7,063,854 B1 for their ability to bind to HLA-A*0201 and stimulate a CTL response for potential use in the method taught by WO 97/26328 A1 for generating allo-restricted CTL with specificity for peptides that are expressed in leukemic cells but not in cells outside the hematopoietic lineage, said allo-restricted CTL useful for adoptive immunotherapy of leukemia patients.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce candidate peptides for research purposes because WO 97/26328 A1 teaches that allo-restricted CTL that are specific for peptides that are expressed on leukemic cells but not in cells outside the hematopoietic lineage are useful to treat patients with leukemia and that such a use is not expected to cause any problems due to possible loss of normal bone marrow cells because these patients are frequently treated with bone marrow transplantation from healthy donors, The Leukocyte Antigen Fact Book teaches that the human CD45 protein is found on all cells of hematopoietic origin and Sievers teaches that CD45 is a target antigen for the majority of leukemia cells as well as for normal stem cells. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 97/26328 A1 teaches that allo-restricted CTL that are specific for peptides that are expressed on leukemic cells but not in cells outside the hematopoietic lineage are useful to treat patients with leukemia and that such a use is not expected to cause any problems due to possible loss of normal bone marrow cells because these patients are frequently treated with bone marrow transplantation from healthy donors, and The Leukocyte Antigen Fact Book teaches that the human CD45 protein is found on all cells of hematopoietic origin.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because WO 97/26328 A1 teaches the method using peptides from target antigens such as WT1 and the usefulness of the method in treating leukemia, Sievers teaches that CD45 is a target antigen for the majority of leukemia cells as well as for normal stem cells and the usefulness of targeting CD45 to treat leukemia, US 7,063,854 B1 discloses that CD45 peptide is capable of eliciting a CTL response and using peptides from anther leukemia antigen WT1 that bind to class I or class II MHC in the same pharmaceutical composition to treat leukemia. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in

order to generate peptides as per the disclosure of U.S. Patent No. 6,602,510 B1 using the human CD45 protein sequence taught by The Leukocyte Antigen Fact Book to use in the method taught by WO 97/26328 A1 of identifying peptides that can bind to alleles present in high frequency in the population such as HLA-A0201 for generation of allo-restricted CTL that are useful in treating leukemia patients.

Applicant does not argue this rejection in Applicant's amendment filed 3/21/07, however, Applicant does argue the references cited herein in combination with other references as applied to the other rejection enunciated supra in this Office Action at item #5.

Applicant's arguments to the references cited in this rejection have been fully considered, but are not persuasive.

Applicant's arguments are of record in Applicant's amendment filed 3/21/07 on pages 8-23 under the section entitled "Rejection Under 35 U.S.C. 103(a)."

It is the Examiner's position that Applicant is arguing the references separately. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It is the Examiner's further position that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention because: (1) WO 97/26328 A1 teaches administering allo-restricted allogeneic CTL specific for peptides from self protein that are expressed in tumors and in a limited number of normal cells, tissue-specific differentiation antigens, and in the case of treating leukemia, adoptively transferring CTL with specificity for leukemias, said CTL generated against peptides that are expressed in leukemic cells but not in cells outside the hematopoietic lineage and WO 97/26328 A1 further teaches identifying new peptides that bind to a particular HLA class I molecule; (2) The Leukocyte Antigen Fact Book teaches that CD45 proteins are found on all cells of hematopoietic origin except erythrocytes and teaches the amino acid sequence of the human CD45 protein; (3) Sievers teaches that CD45 is a target antigen for the majority of leukemia cells; (4) '510 discloses an epitope prediction algorithm to predict peptides that bind to a particular HLA class I molecule, and methods to test for said binding and methods to test for CTL stimulating activity and immunogenicity, and the relationship of affinity to immunogenicity, as well as disclosing an HLA-A2 supermotif for peptides that bind to HLA-A2, HLA-A3 and HLA-B7, three alleles for which broad, non-ethnically-biased population coverage may be obtained; and (5) '854 discloses a CD45 peptide antigen capable of stimulating T cells, prediction of HLA-A2 binding peptides from another leukemic cell derived peptide antigen WT1, testing those peptides for binding to HLA-A2, and testing their ability to function as CTL epitopes.

It is the Examiner's position that WO 97/26328 A1 does not teach away from using membrane bound cytokine receptors such as CD45 because it teaches other proteins that are intracellular DNA binding proteins, and Sievers teaches that CD45 is a target antigen for the majority of leukemia cells. It is the Examiner's position that motivation for combining the prior art elements may be found in the teaching of Sievers teaches that CD45 is a target antigen for the majority of leukemia cells, the disclosure of '854 that a CD45 peptide can stimulate T cells, and in the disclosure of WO 97/26328 A1 that teaches adoptively transferring CTL with specificity for leukemias, said CTL generated against peptides that are expressed in leukemic cells but not in cells outside the hematopoietic lineage (as is CD45) and further teaches identifying new peptides that bind to a particular HLA class I molecule. '510 and '854 disclose that it is routine in the art to predict HLA-A2 binding peptides, test them for binding to HLA-A2 and for their ability to stimulate CTL.

With regard to Applicant's argument to an alleged misreading of Gaiger, it is the Examiner's position that 854 discloses a CD45 peptide antigen capable of stimulating T cells, prediction of HLA-A2 binding peptides from another leukemic cell derived peptide antigen WT1, testing those peptides for binding to HLA-A2, and testing their ability to function as CTL epitopes. Further, it is the Examiner's position that Sievers teaches that CD45 is a target antigen on leukemia cells, and '854 teaches a CD45 peptide that can generate a Th response presumably to provide T cell help for antibody production as well as for CTLp to CTL stimulation and '854 further teaches peptides from another leukemia cell target antigen that are Th or CTL epitopes.

With regard to Applicant's arguments to the variants of SEQ ID NO: 1, said variants are non-elected species and have not been examined.

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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